FACTORS FAVORING THE ONSET AND CONTINUATION OF RHEUMATIC FEVER*

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During the past three decades our ideas concerning rheumatic fever have undergone striking evolution, as evidenced by the change in nomenclature from acute articular rheumatism to acute rheumatic fever, and finally to rheumatic fever. True it is that the older terms still hold, and rightly so when used to describe particular forms of the infection; but too often one is employed synonymously with another. It is unfortunate that with increasing knowledge of the condition there cannot be devised a new term sufficiently extensive to embrace all of its manifestations, yet distinctive enough to separate it as a nosological entity. The introduction of the terms "infectious rheumatism" (1) and "rheumatic granulomatosis" (2) are attempts in this direction; but having only pathologic or bacteriologic significance they offer little if any advantage over the term rheumatic fever, which at least has background in clinical experience.

Objections to the use of this term are twofold: (i) The adjective "rheumatic" to most persons signifies arthritis or muscular pain; and (ii) some of the manifestations of activity—notably chorea—are frequently not accompanied by fever. To this one may reply, first, that the original meaning of the term "rheuma" was a morbid process flowing from one organ or tissue to another; hence it still retains its descriptive value; and, second, that regular consistent use of the thermometer would reveal some degree of

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pyrexia during certain periods of most attacks; therefore, fever still remains one of our most valuable guides of persisting infection.

Another point deserves attention; if the term rheumatic fever is substituted merely for the expression, acute articular rheumatism, our nomenclature has suffered a loss, because the second signifies acutely swollen joints. When, on the other hand, it is used to include all of the manifestations of the infection in the same manner as tuberculosis includes all types of the disease induced by the tubercle bacillus, then does it have distinct descriptive value.

To many it seems well to delete the word "acute" because in the majority of cases the infection is long standing. Only when rapidly fatal, or in those cases with a monocyclic course may the adjective acute be properly applied, but even then we must be certain that the infection has become permanently inactive. For example, we do not picture syphilis as acute even though the roseola disappears within two weeks; likewise it may be better not to use any single manifestation of rheumatic fever as an index of chronicity.

Historically the conception of rheumatic fever began with rheumatic polyarthritis; a century has elapsed since the recognition of the importance of involvement of the valvular endocardium; fifty years ago the nature of the subcutaneous nodule was noted; twenty-five years later its analogue in the submiliary myocardial nodule—the Aschoff body—was described; and within the past decade the extent of the vascular lesions has been appreciated. In the meantime, with an improvement in the general economic state of society, together with extensive use of salicylates the clinical picture has apparently changed. Hyperpyrexia rheumatica has become a medical curiosity, and according to old clinicians rheumatic polyarthritis is less severe. But whether there has been a corresponding amelioration in carditis and chorea one may well doubt. Knowledge gained from contemporary graphic methods of recording

cardiac abnormalities renders difficult comparison with statistics obtained in other ways; but figures such as presented by Ehrström and Wahlberg (3) in Helsingfors indicate that there has been no diminution in the incidence of chronic rheumatic heart disease from the administration of salicylates, and according to recent statistics it still seems that rheumatic fever is the largest single factor in the causation of heart disease (4).

May it not then be of greater value to apply another method of historical approach, beginning in childhood and following the various manners of the unfolding of the infection, rather than to orient ourselves from the disease in adults where it is less frequent even though more acute, and where severe cardiac damage is relatively less common.

But before tracing the clinical course it may be well to reconstruct a background of histopathological tissue changes. What does the microscope show us concerning the nature of the infection? Aschoff's description of the submiliary nodules arising in the loose connective tissue septa in the myocardium furnished a structural archetype to which alterations in other tissues might be compared. The discussion which has centered about this nodule has at times diverted attention away from the fact that other lesions, possibly not quite so regular in their cellular structure, might be just as characteristic. One need only mention the subcutaneous nodule. The important factors to recall are the type of tissues and organs involved, and the manner of evolution of the lesions; one may then attempt to construct from these factors or elements a hypothesis of the nature of the infection.

In the Aschoff body there is a minute central area of broken collagen fibers, surrounded by large cells probably derived from locally stimulated connective tissue. At times there are seen polymorphonuclear cells, lymphocytes and plasma cells; and finally fibroblasts leading eventually to a scar. The subcutaneous nodule shows qualitatively similar tissue injury and cellular response, but with different

quantitative distribution of the component parts; the connective tissue degeneration is often more massive, the groups of large mononuclear cells are more numerous. Frequently a large nodule is apparently formed as a conglomeration of smaller nodules. In places large basophilic mononuclear cells seem to arise from vessel walls. Relatively few polymorphonuclears are present. If now we examine the joints another but related picture appears. The periarticular tendons and ligaments show numerous microscopic areas in the form of nodules or tongues, most having necrotic centers and surrounding proliferated cells. The synovia shows palisading of its lining layer, and minute foci with central necrosis with surrounding collars of cells. Diffuse infiltrations of polymorphonuclears are common. The periarticular tissues are infiltrated with serum which in part contributes to the familiar swollen joint; and there is destruction of muscle fibers at the musculotendinous junctions (2, 5, 6). In other words, the minute focal and vascular lesions about the joints are numerous and exudation is widespread. Involvement of the pleura and pericardium shows similar exudative tendency, but in the substance of these membranes are often foci comparable with the Aschoff bodies. In the auricular endocardium there are similar tissue and cellular changes, but these are arranged in streaks and plaques without interruption in the continuity of the lining endothelium (7, 8a). In the valves on first sight appears another picture, for the endocardium is broken and thrombotic verrucae are often, though not always, laid down at the site of impact of the leaflets. But throughout the substance of the valve and in the chordae may often be seen broken collagen material, proliferative cells and infiltrations like that of the auricular endocardium; at times they are arranged in typical Aschoff bodies. As so beautifully shown by Von Glahn and Pappenheimer (9) and others, many portions of the vascular system are similarly involved. In the aorta focal lesions follow branches of the vasa vasorum; but smaller arteries have areas of end- and mesarteritis, always accompanied by focal destruction of connective or elastic tissue. In the

peritonsillar, nasopharyngeal and intestinal blood vessels Holsti (10) has demonstrated extensive endarteritis verrucosa. In the peritonsillar capsule near the points of attachment of the pharyngeal muscles MacLachlan and Richey (11), Gräff (12) and others have described areas very similar to Aschoff bodies, and also in the tongue about the lingual tonsils. Gräff applies the term "primary complex" to these peritonsillar lesions because of their hypothetical rôle as sites whence the infectious agent is distributed to other parts of the body. He thinks that the pathological condition of the blood vessels supplying these lesions favors such a distribution.

The striking picture of the Aschoff body cells has, moreover, attracted attention away from what appears to be the initial injury to the connective tissue fibers. Von Glahn and Pappenheimer have frequently described the granular broken appearance of these fibers, and many have seen the fibrin-like staining infiltration in the foci; but recently Klinge (13) claims that the primary change is a minute focal "fibrinoid swelling" of the intercellular mesenchymal ground substance; which swelling leads secondarily to a fraying out and altered staining reaction of the collagen fibers and fragmentation of the elastica. He also describes waxy degenerations of individual muscle fibers with secondary proliferation of the perimysium.

It thus appears that rheumatic fever instead of affecting any one set of organs is a disease primarily of the connective tissue, or, in Hueck's (14) words, of the mesenchymal system. Those structures composed chiefly of connective tissue, and specially subject to functional stress and strain and undergoing active motion appear to be the most vulnerable. Interference with the function of these moving structures may, however, detract attention from unobtrusive lesions in other organs, such as recently described by Paul (15) in a rheumatic perihepatitis with characteristic lesions in the underlying blood vessels. Rheumatic vasculitis in the kidneys has been described by Fahr (16), Evans (17) and others; and symptoms of appendicitis, in-

timately associated with generalized rheumatic fever, point to a similar involvement of at least one portion of the intestinal tract. A constantly growing literature on pulmonary lesions in this disease indicates also how the lower as well as the upper portion of the respiratory tract may be involved.

A knowledge of the numerous points and tissues where the infectious agent attacks the body gives us another standard with which to judge rheumatic fever. If so many organs or tissues are simultaneously involved, there is every reason to suppose that they may also be individually and successively implicated. In fact, pediatricians have long appreciated the tendency of children to show first one and then another of the so-called rheumatic series (18); and that not until after the lapse of years might enough members of this series have appeared to render certain a diagnosis. Monosymptomatic signs of disease are difficult of interpretation unless sufficiently characteristic to have diagnostic specificity; for example, the various cutaneous syphilides. But in order to form correct judgment concerning visceral lesions it is often necessary to have concomitant clinical signs or specific laboratory aids.

Unfortunately in the case of rheumatic fever no specific laboratory test is at hand; some of the concomitant, easily visible manifestations, such as tonsillitis, are too non-specific to furnish much needed assistance. But in these very non-specific signs we may possess most important aids to understanding the nature of the infection; and in tracing the life history of rheumatic fever it is essential to note their occurrence and then try to interpret their influence upon the course of the malady.

The causation of many chronic diseases is usually the algebraic sum of a number of factors rather than the exclusive action of any one. Infection is the result of interaction between an animal host and an infecting parasite in which many variables are too subtle for laboratory measurement. Moreover, the study of the life history of

chronic disease in the patient gives us many useful hints as to the nature of the illness, and often furnishes therapeutic indications. For example, we now know that the presence of tubercle bacilli in a body does not necessarily indicate active tuberculosis. Certain environmental conditions favor the spread of the lesions, others favor their regression. Indeed, a study of these latter conditions has furnished us with some of our most important weapons against this disease; and comparable knowledge may conceivably have a similar effect in rheumatic fever.

Geographically the disease seems to be essentially one of the temperate zone. Clarke (19) has recently marshalled most convincing evidence indicating that in the true tropics it is 15 to 20 times less frequent than in Europe. Studies by the Seegals (20) indicate, moreover, that the infection is less common in the southern part of this country; and observations (21) from New Orleans show that when present in the South it runs a milder course than in the North. The ultimate effect of removing rheumatic subjects to hot or dry climates is, however, still a matter for investigation.

Statistics also show that obvious rheumatic fever is from fifteen to twenty times more frequent among the laboring classes than in those forming the bulk of private practice. But many physicians can testify concerning its existence and tendency to progress in patients living under apparently ideal home surroundings. Another viewpoint has been advanced to the effect that among persons in better economic conditions the infection may have relatively more monosymptomatic forms and hence lead more frequently to cardiac damage without obvious general symptoms.

Infants and very young children are relatively free from the disease, and, even though cases appear in children of from two to four years, the curve of frequency of first attacks does not begin its steep ascent until about the age of five or six years. It then rises steadily until the period from

nine to eleven years when it begins to fall; first attacks are relatively much more rare in adults than in children. The studies of Wilson, Lingg, and Croxford (22) indicate, moreover, that children suffering from the infection tend to have fewer obvious relapses after the age of eleven or twelve years. Thus a condition of resistance seems to begin to develop about the age of puberty. But the period of greatest incidence of new cases during the first few years of school life is worthy of emphasis. Is it the result of intimate contact like that seen in measles, or is it due to an age-linked hypersensitiveness? The experience of many observers teaches that the infection is progressing steadily in the hearts of many children while avoiding other organs. For example, Sutton (23) found in the Bellevue Hospital 18 per cent of 427 rheumatic children to have well developed rheumatic carditis without a previous history of either polyarthritis or chorea.

An apparent precursory factor in a majority of cases is repeated infection in the respiratory tract, often in the form of tonsillitis, sinusitis, middle ear disease, or bronchitis. In our experience so frequent has been the occurrence of acute tonsillitis within from one to five weeks of an acute attack that we now date the duration of a given attack from the onset of tonsillitis. But more detailed investigation of the previous state of health of patients usually reveals an earlier history of repeated sore throats, otitis media, or of recurring or almost continuous sinusitis. Not infrequently closer questioning discloses mild joint or growing pains with these upper respiratory infections. Coates and Thomas (24), Coates and Coombs (25), and Vining (26), all report the finding of small subcutaneous granules in a fairly high percentage of school children. Whether or not these are genuine rheumatic subcutaneous nodules is a moot point; but their alleged demonstration by serious students of the disease should stimulate renewed investigation, because extensive painless nodules have been frequently observed in children having no other symptoms of sufficient severity to incapacitate them.

Other conditions in many children preliminary to an acute attack are loss of weight, anorexia, and general signs of mild intoxication. To these Vining has applied the term "toxic debility," and found that many of his rheumatic youngsters had in addition a history of intestinal disturbance of sufficient severity to point to the intestinal tract as an area whence the infectious agent might be spread throughout the body. The greater liability of children of the poorer classes to suffer disorders of malnutrition or to be deprived of certain accessory food substances suggests that possibly these are elements leading to a higher incidence of the disease among such individuals compared with people living on a higher economic scale. Recent studies of rheumatic children in out-patient departments furnish additional support concerning the influence of nutrition in that loss of weight has been found to be one of the most common precursors of a relapse.

Recurrences of symptoms sufficiently severe to be called true relapses are commonly observed in children year after year; but symptoms and signs too mild to attract much attention not infrequently occur between relapses. For example, Shapiro (27) has recently noted electrocardiographic evidence of active cardiac damage in at least 60 per cent of 119 school children following apparently complete recovery from an acute attack; and Levy and Turner (28) have recorded electrocardiographic abnormalities weeks and months before the onset of acute symptoms. Persistent lowgrade leucocytosis, unexplained on grounds other than that of persisting rheumatic infection, is not infrequent. Several of our patients have observed recurring erythema marginatum for months without appreciating its significance until more incapacitating manifestations forced them to seek hospital care, and the continuance of this peculiar rash for weeks or months following subsidence of acute arthritis not infrequently is an index of continuing infection.

Not only are such pictures seen in children, in whom we have learned to expect repeated relapses, but a similar history is not rare in adults, when sought with sufficient care.

For example, a man, aged 33 years, in good circumstances gave a history of acute tonsillitis in 1929 followed by acute rheumatic polyarthritis; then by tonsillectomy. In the winter of 1930 he had sore throat followed by a similar polyarthritis. But more careful questioning revealed repeated pharyngitis for eight to ten years previously, several attacks of sinusitis and recurring pain in the neck and back of sufficient severity to make movements difficult. It does not appear unreasonable to suppose that during the previous years he was suffering from mild rheumatic infection which was not brought to acute intensity until his first attack of severe tonsillitis. Such histories are not rare.

That tonsillitis plays an important rôle in precipitating many acute attacks of rheumatic fever we can accept as fairly well established. Where both diseases are reportable, the peak of the curve of the former antedates that of the latter by about two weeks. Glover (29), in presenting details concerning several concomitant epidemics of these two conditions, advances the theory that they are spread by droplet infection which must reach a certain intensity before the resulting diseases reach epidemic proportions. In one outbreak carefully studied, the carrier rate for meningococci and the incidence of cerebrospinal meningitis and of rheumatic fever, ran parallel; and this suggests that similar influences were at play in causing an increase in all three conditions. With a diminution in crowding there was a disappearance of both diseases, and with renewed crowding there was a return of an equal number of each. While these appeared to be primary attacks of rheumatic fever, one would like information concerning the previous history of the rheumatic individuals. Such questions are raised by the study of epidemics among children with rheumatic heart disease or convalescent from rheumatic fever, such as reported by Boas and Schwartz (30), and Hiller and Graef (31). In the first epidemic reported by the former group there were four cases of bronchopneumonia accompanied by rheumatic carditis, and one of acute

tonsillitis; in the second, although the precursory respiratory infection was not so marked, still acute rheumatic exacerbations developed in six boys in rapid succession. Among 19 non-rheumatic children in the same wards, none suffered from rheumatic fever, while in 22 previously rheumatic subjects 11 developed acute rheumatic fever. In the epidemic reported by Hiller and Graef there were 43 children exposed, of whom 39 probably were previously rheumatic. Within five days of arrival at the camp there were 12 cases of upper respiratory infection, and within five weeks 10 cases of polyarthritis, one of chorea, two of bronchopneumonia, one of acute bronchitis, and one of tonsillitis, pericarditis and pneumonia. Unfortunately the exact relationship of the upper respiratory infections to polyarthritis in each case was not recorded; nevertheless the high incidence of acute exacerbations of the disease in previously rheumatic children is worthy of emphasis, as is also the occurrence of severe pulmonary infection.

Scarlet fever is another disease intimately associated both with first attacks and with relapses of rheumatic fever. Some clinicians state that this disease in previously rheumatic children is practically always followed by acute manifestations of rheumatic fever. This suggests the possibility of comparable influences in all of the above mentioned epidemics, namely upper respiratory infection.

I realize fully the possibility of at least two interpretations of the phenomena described: (i) That rheumatic fever may be due to an unknown virus which may long lie latent in the body, and be incited to renewed activity because of the depressing influence of the acute respiratory infection. (ii) On the other hand, it is possible that repeated and persisting low-grade infections induce or are accompanied by tissue changes too mild to be dignified by the name rheumatic fever, and that only with a stormy acute infection such as tonsillitis, or with invasion of the pulmonary tract by streptococci are the accompanying morbid processes raised above the clinical horizon. In

either case the conditions existing prior to the attack of acute rheumatic fever are worthy of more detailed study than they usually receive.

To illustrate this point let us consider another group in which a contagious element may exist: the family. Since St. Lawrence's (32) report eight years ago showing the incidence of multiple cases of rheumatic fever in a group of families to be as high as that of tuberculosis, there have been several confirmatory studies. It now appears that in a rheumatic family with one case the probability of occurrence of a second case is three or four times as great as in a family previously free from the disease. Although the various factors favoring the development of rheumatic fever may be almost as difficult of analysis within a family as in any other group, the family as a unit offers a promising field for investigation. For example, several years ago we learned that the mother of one of our rheumatic children frequently had sore throats within a short time of the appearance of relapses in the child. Following the removal of badly diseased tonsils in the mother her attacks of sore throat ceased and since then the child has been free from recurrences. Last winter a boy was admitted to the hospital with the following recent history of acute infections in himself, his mother and sister:

1st day Onset of "grippe" in patient and sister.
5th day Patient better; sister developed rash.
8th day Mother developed "grippe" with severe pain in back; sister recovered and lost rash.
12th day Mother recovered.
14th day Patient developed fever and beginning polyarthritis.
16th day Patient had evidence of severe myocarditis.
19th day Patient had signs of pericarditis.

Such a history of contagion reminds one of the concomitant respiratory infections in the epidemics mentioned above, and suggests the possibility of atypical non-diagnostic manifestations in the sister and mother. Indeed, a correlation of all of the illnesses of the members of fifteen rheumatic families by Paul and Salinger (33) has already yielded important data along these lines. They have shown

that both primary and secondary attacks of rheumatic fever in certain members of a family have been accompanied by the simultaneous appearance of recognizable rheumatic fever in other members of the family, and not infrequently by the appearance of such non-specific affections as sore throat, bronchitis, bronchopneumonia and skin rashes. They found in addition that the disease spread more frequently to the children under twelve years of age than to the older children and adults. Another striking feature among these families was the frequency with which so called non-specific respiratory infections occurred before the appearance of characteristic rheumatic fever. If an extension of this type of investigation yields similar data, we shall be in a position to formulate preventive measures not heretofore applied. Indeed, the information already available from the several reports above reviewed together with those of Andrieu (34), Grenet (35), Irvine-Jones (36) and others suggests strongly the communicable nature of the infection. The time when health authorities will recognize this feature of the disease and attempt to assemble data compiled from compulsory notification may be nearer than we can now foresee. The numerical and economic importance of the problem far outweighs that of poliomyelitis, encephalitis, leprosy, and many other reportable diseases.

One more feature deserves attention; the hypersensitiveness of patients with rheumatic fever to streptococcal products, which has been found by most observers to be higher than in any other disease. One must admit that such hypersensitiveness is found in many non-rheumatic persons; hence these skin tests have not diagnostic specificity. But it has offered a possible explanation of certain peculiarities of the disease (37). Mackenzie and Hanger (38), Kaiser (39), and Ando (40) have all shown this type of hypersensitiveness to be rare or absent in infancy and to increase in relative frequency with each half decade up to the period of adult life. In Duckett Jones' (41) experience over 95 per cent of rheumatic children have positive reac-

tions to a filtrate of a single strain of indifferent streptococci. Derick and Fulton (42) have recently found skin hypersensitivity to hemolytic streptococcal nucleoproteins in 88 per cent of rheumatic children between six and ten years of age compared with only 12 per cent in non-rheumatic children, surely a most significant difference, when it is noted that 88 per cent of their entire group of rheumatic fever patients gave positive reactions. It thus seems that hypersensitiveness to streptococci which appears with advancing years in many individuals occurs much earlier in rheumatic fever patients. Probably the repeated respiratory infections already so frequently mentioned are factors in conditioning a high sensitivity to streptococci; and it does not seem improbable that the condition recognized as acute rheumatic fever is incited by intense, focal infections such as acute tonsillitis, or otitis media—both due to hemolytic streptococci—occurring in already somewhat hypersensitive bodies. On the other hand, it must be recognized that we do not know definitely whether the relationship between streptococcal hypersensitiveness and rheumatic fever is causal or merely concomitant. Its existence, however, gives us a definite point of attack (43), for could we influence it in one direction or another we would have an index with which to judge the effect of certain therapeutic efforts.

Summary

Rheumatic fever is economically one of the most important diseases, not only because of its acute manifestations, but also because of its rôle in the production of between 30 and 40 per cent of chronic cardiac disease in the latitude of the North Atlantic States. Microscopic findings indicate it to be a wide-spread disease involving by preference mesenchymal structures or mesenchymal portions of parenchymatous organs. Physiological stress and strain appear to favor localization of its manifestations, although it may be locally active without giving rise to symptoms; and various vulnerable organs may be either simultaneously or independently involved.

A number of factors appear to have causative relationships. Climatic conditions such as exist in temperate zones in winter favor its development; while sunny dry summers and tropical weather inhibit or prevent its evolution. Among the poorer classes it is from 15 to 20 times more prevalent than in persons better housed and fed. Malnutrition and mild toxic states are frequent precursors of characteristic attacks. Most patients, both children and adults, give a history of repeated non-specific infections of the respiratory tract, tonsils, sinuses, or middle ear, extending over several years, before a typical attack of rheumatic fever is ushered in by a severe focal infection. Persons in intimate contact with patients during acute outbursts of rheumatic fever not infrequently suffer simultaneously from upper respiratory infections, or from typical rheumatic fever; hence there seems to be a distinct communicable factor favoring its spread. Because chronicity and relapses are so frequent, and crippling cardiac damage is of such gradual evolution, and finally because laboratory tests often reveal activity in periods between attacks, it seems justifiable to consider the infection to be characterized by long periods of preparation or sensitization of the tissues, the result of repeated mild infection before a more intense focal infection sets off the violent explosion recognized as acute rheumatic fever. Similar mild infections, moreover, apparently favor the continuation of true rheumatic activity in viscera already involved. It seems logical, therefore, to regard these preparatory periods and mild chronic infections between acute outbreaks as essential parts of the morbid process; hence our therapeutic and prophylactic efforts should be directed against them as well as against the more acute manifestations of the disease.

NOTE—While this article was in press the monograph (44) of Coburn appeared which presents much valuable additional evidence concerning the chronic and contiguous nature of rheumatic fever; its geographic distribution; the high degree of cutaneous sensitivity of rheumatic fever

patients to hemolytic streptococcal nucleoprotein; and finally, a striking parallelism between an increase of hemolytic streptococci in the upper respiratory tract and relapses in patients with the disease. He apparently wishes to designate the malady as the "rheumatic state" and only recognizes "rheumatic fever" when it is diagnostically clear cut.

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